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A Comparison of Early Effects with Two Dose Rates in Brachytherapy of Cervix Carcinoma in a Prospective Randomised Trial

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This phase III randomised trial examined the early effects of two low dose rates (0.38 and 0.73 Gy/h) in brachytherapy of stage I and IIp cervical cancer patients. A total of 204 patients were included between January 1985 and September 1988. Since the main analysis of this paper concerned surgical difficulties, only the 155 patients (76%) on whom surgery was performed at the Institut Gustave-Roussy were retained in this analysis. Treatment consisted of uterovaginal ^{137}Cs irradiation followed by immediate or deferred surgery. The two groups were similar for pretreatment characteristics except for endocervix involvement. Their brachytherapy parameters were also similar (60 Gy pear dimensions, doses to critical organs, total kerma, etc.). The factors with a poor prognosis were, for surgical difficulties, older age, stage II and a small irradiated pear volume; for difficulties with haemostasis, immediate surgery, stage II and previous surgery; and for difficulties in dissection, lymph node involvement. The dose rate significantly influenced surgical difficulties for the stage IIp patients operated on by deferred surgery. Those treated with the higher dose rate showed a 2-fold increase in surgical difficulties compared to those irradiated at the lower dose rate ($P = 0.03$). The independent prognostic factors for sterilisation of the surgical specimen were small tumour size and absence of lymph node involvement. An inverse dose rate effect was observed for medium size tumours, with significantly more sterilisations observed in stage IIp patients in the lower dose rate group ($P < 0.01$).

Key words: cervical carcinoma, low dose rate, phase III trial, surgical difficulties, tumour sterilisation
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INTRODUCTION

ONE OF the treatments of reference in stage I and II cervical cancer patients is a radiosurgical approach involving brachytherapy followed by surgery [1–6]. For essentially historical reasons, the cervix carcinoma brachytherapy system of Paris is classically administered at a dose rate of 10 Gy per day for 6 days up to a total dose of 60 Gy. In order to improve the comfort of the patient and to decrease the overall treatment cost, there is a strong temptation to decrease the brachytherapy time, which would as a consequence increase the dose rate.

Experimental studies *in vivo* and *in vitro* have taught us that the effects of an increase in the dose rate of ionising radiation, that is applying the same total dose in less time, are increased in varying degrees from one tissue to another [7, 8]. The sparing effect of a low dose rate is particularly effective on late responding tissues such as nervous tissue and sub-mucosa. Several clinical studies have been published on this subject, most of them non-randomised retrospective studies on a small number of patients [9–14]. Moreover, their conclusions are contradictory. Before this study was undertaken, the Brachytherapy Department at the Institut Gustave-Roussy (IGR) purchased more active Caesium (Cs) sources, allowing the treatment of patients in 3 days rather than the usual 6 days with the same total doses. Soon afterwards, the surgeons began to notice more surgical difficulties, and wondered whether something had changed in the way these patients were treated before coming into surgery. In fact, the only difference was the dose rate patients received during brachytherapy. In contrast, a preliminary trial with 27 patients did not show any difference in the rate of surgical difficulties when retrospectively compared to a historical series [15]. It thus seemed necessary to undertake a prospective randomised clinical trial.

The objective of this trial was to determine whether gynaecological brachytherapy can be applied in 3 days instead of the

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usual 6 days, and still achieve similar results. This would have a theoretical, radiobiological (validation of models derived from radiobiology), as well as a practical interest (decrease treatment time by permitting a shorter hospital stay with better tolerance for the patient, and a rationalisation of hospital resources). This paper focuses on the early effect of brachytherapy, in particular the effect of the dose rate on the surgical difficulties and the sterilisation of the surgical specimen.

MATERIALS AND METHODS

Patient selection

All operable patients presenting histologically verified cervical cancer (stage Ib or stage II proximal-IIp) were considered eligible. Patients were excluded if they had a history of another cancer, pelvic irradiation or had been previously treated for cervical cancer at another institution.

Stages I and II were included with a distinction between proximal and distal stage II (i.e. between operable and inoperable). Stage was determined under general anesthesia by at least two specialists. We considered stage Ib to be a tumour macroscopically restricted to the cervix. Stage IIp was defined as a cervical carcinoma with involvement of the upper third of the vagina and/or the inner third of one or both parametrias. Staging investigations also included full blood counts, basic blood chemistry (ionogram, creatinine liver tests, etc.), chest X-rays and intravenous urograms. Lymphangiography was carried out in patients with tumours having a maximum dimension of 5 cm or more, unless there were medical contraindications or the procedure was technically impossible. Fitness for surgery was subject to an assessment by an anaesthetist.

Treatment regimen

Stages Ib and IIp cervical cancers are treated at the IGR by uterovaginal brachytherapy, followed by radical colpohysterectomy combined with bilateral external iliac lymphadenectomy. Details of the brachytherapy have been published [16–18]. Briefly, the treatment was adapted to the vaginal cavity and tumour anatomy of each patient, using a system of customised vaginal mold and ^{137}Cs sources, ranging in length from 16 to 80 mm, after-loaded with a Curietron. The vaginal mold and a flexible uterine applicator of appropriate length were inserted under general anaesthesia. Computerised dosimetry was routinely performed in three planes, based on two orthogonal X-rays. This dosimetry allowed accurate calculation of the doses to the various ICRU (International Commission on Radiation Units and Measurements) reference points (bladder, rectum, pelvic walls and lymphatic trapeze) [19]. The treatment volume was tailored to the "minimal 60 Gy volume" defined by the lengths, width and thickness of the volume encompassed by the 60 Gy isodose curve, and recalculated in cm^3 by a three-dimensional computerised dosimetry. The radiotherapist chose the application time for each source so as to optimise the distribution within the target volume, while minimising the dose to the surrounding normal tissues (especially the bladder and rectum). If the greatest tumour dimension was over 4 cm, the brachytherapy was preceeded by 20 Gy of external irradiation or was delivered in two sessions 3 weeks apart. Ideally, the patients underwent surgery 6 weeks after the end of brachytherapy. At this time, the congestive phenomena occurring immediately after irradiation had disappeared, and postradiation sclerosis was sufficiently inconspicuous so as not to interfere with surgery [20].

Patients for whom lymph node invasion was suspected [lymphography, computed tomography (CT) scan] underwent surgery immediately after brachytherapy. Once the lymph node invasion had been revealed or confirmed histologically, supplementary pelvic external irradiation (25 sessions of 1.8 Gy) was applied, with a central lead block shielding the area that had been treated by brachytherapy.

Randomisation

All the patients with stage Ib or IIp cervical cancer were entered into the IGR Biostatistics Department database, but only patients meeting the eligibility criteria were randomised. Patients were randomly assigned to one of the following brachytherapy schedules:

—Group A: 0.38 Gy/h; source with a mean activity of 30.5 $\mu Gy\ h.m^2$ cm giving a reference isodose of 60 Gy in an average period of 6–7 days.
—Group B: 0.73 Gy/h/; source with a mean activity of 52.4 $\mu Gy\ h.m^2$ cm giving a reference isodose of 60 Gy in an average period of 3–4 days.

The radiotherapist prescribing the dose was not aware of the activity chosen by the randomisation. The time of application for each source was selected on the basis of dosimetry performed with an arbitrary reference activity of 34.9 $\mu Gy\ h.m^2$ cm. The technical staff recalculated the treatment time required according to the actual activity by means of a simple equation. Thus, if the radiotherapist had selected a time of 5.3 days for the reference activity of 34.9 $\mu Gy\ h.m^2$ cm, the total irradiation time for an activity chosen by randomisation of 52.4 μGy would be $(5.3 \times 34.9)/52.4$ or 3.5 days.

Surgical difficulties

For each patient, just after the operation, the surgeon filled in a questionnaire containing information about haemostases and difficulties in dissection (vesico-vaginal, recto-vaginal and parametrial). A patient presenting at least one of these problems was considered a case of surgical difficulty. The surgeon was also asked to guess the dose rate group to which she belonged, without prior knowledge of the randomisation. These criteria were only evaluated for patients operated at IGR.

Anatomopathology

After surgery, all the anatomopathological slides were reviewed by the same team of pathologists at the IGR. The cervix was cut sagittally every 5 mm to evaluate the presence and quantification of residual cervical tumour [21]. The pathologist also indicated the presence of node involvement.

Statistical analysis

Patient characteristics were compared between treatment groups using the χ^2 test for categorical variables, and Student's *t*-test for continuous variables. Surgical difficulties and sterilisation were analysed with logistic regression models. Comparisons between treatment groups were adjusted for prognostic factors and concomitant variables.

RESULTS

Accrual and eligibility

A total of 204 patients were randomised between January 1985 and September 1988. The accrual rate remained constant, at about 60 patients per year, throughout the trial. The mean follow-up time, calculated as the number of months elapsed between randomisation and the latest information for patients

known to be alive, was 42 months (range 1–78). A total of 4 patients did not fully comply with the eligibility criteria defined in the protocol: preoperative stage III (1 case), preoperative stage IVb (1 case), previous medical history of breast cancer (1 case) and previous administration of chemotherapy for pelvic adenopathy associated with cervical carcinoma (1 case). However, these 4 patients were kept in the analysis.

Since the main results of this paper focus on surgical difficulties, only the 155 patients (76%) for whom surgery was performed at IGR were retained in the analysis. The characteristics of these patients are summarised in Table 1.

The two treatment groups were not significantly different for pretreatment characteristics, except for endocervix involvement, which was observed to be more frequently invaded in the higher dose rate group ($P < 0.02$).

Protocol deviations

One patient randomised to the 0.73 Gy/h treatment group was given the lower dose rate because a suitable radioactive source was not available. Brachytherapy was considered incomplete in 7 cases for the following reasons: early removal of the vaginal mold because of abdominal pain (1 case), psychological intolerance (1 case), early removal of the uterine tube because of abdominal pain (1 case), inability to retain the uterine tube (2 cases) or vaginal mold tube (2 cases) in position. Protocol deviations were similar between the two groups (15 and 13 patients in each treatment group, respectively). For the analysis of this trial, patients were kept in the group to which they were randomised.

Treatment administration

Prebrachytherapy external radiotherapy was administered to 42 patients who each received a total of 20 Gy in 10 sessions at the rate of 2 Gy per session (Table 2).

Table 1. Demographic characteristics (patients with surgery at IGR)

	0.38 Gy/h (n = 79)		0.73 Gy/h (n = 76)		P
Age (years)					
< 40	24	(30%)	19	(25%)	
40–59	43	(54%)	43	(57%)	ns
≥ 60	12	(15%)	14	(18%)	
Country of origin					
Metropolitan France	32	(41%)	32	(42%)	
Other	47	(59%)	44	(58%)	ns
Previous surgery	15	(19%)	22	(29%)	ns
Stage IIp	40	(51%)	44	(58%)	ns
Endocervix involvement	36	(46%)	49	(64%)	$P < 0.02$
Histology					
Squamous	72	(91%)	64	(84%)	
Adenocarcinoma	6	(8%)	11	(14%)	
Mixed	1	(1%)	1	(1%)	ns
Largest tumour dimension (mm)					
< 40	35	(44%)	37	(49%)	
40–59	34	(43%)	23	(30%)	
≥ 60	10	(13%)	16	(21%)	ns
Lymph node involvement N +	19	(24%)	27	(36%)	ns

ns, non-significant.

Table 2. Treatment characteristics (patients with surgery at IGR)

	0.38 Gy/h (n = 79)		0.73 Gy/h (n = 76)		P
Pre-brachytherapy radiotherapy					
No	59	(75%)	54	(71%)	
Yes	20	(25%)	22	(29%)	ns
Brachytherapy					
Number of brachytherapy sessions					
1	53	(67%)	47	(62%)	
2	26	(33%)	29	(38%)	ns
One session (days)					
Median duration	6.4		3.3		
Two sessions (median days)					
First session	3.8		2.1		
Second session	3.2		1.7		
Interval between sessions	22.5		20.5		ns
Kerma (cGy.m^2)					
< 4	16	(20%)	15	(20%)	
4–5	22	(28%)	20	(26%)	
≥ 5	41	(52%)	41	(54%)	ns
Pear volume (cm^3)					
< 120	13	(16%)	15	(20%)	
120–179	36	(46%)	28	(37%)	ns
≥ 180	30	(38%)	33	(43%)	
Surgery*					
Deferred	65	(82%)	59	(78%)	
Immediate	14	(18%)	17	(22%)	ns

*Deferred > 6 weeks after end of brachytherapy treatment; immediate, < 1 month after end of brachytherapy treament. ns, non-significant.

Brachytherapy was administered in a single session to 100 patients (65%). The median duration of brachytherapy in these patients was 6.4 days for the lower dose rate group and 3.3 days for the higher dose rate group.

Brachytherapy was administered in two sessions to 55 patients (35%). The median duration of the first session in these patients was 3.8 days for the lower dose rate group and 2.1 days for the higher dose rate group. The median duration of the second session was 3.2 days for the lower dose rate group and 1.7 days for the higher dose rate group. The mean interval between sessions was 22 days in both groups. The dose rate was the only brachytherapy variable which differed between the two groups (Table 2). All other brachytherapy variables were distributed similarly.

Surgery was performed more than 1 month after brachytherapy (deferred surgery) in 124 patients (80%). The most common cause for immediate surgery was preoperative diagnosis of suspected adenopathy at lymphography and/or CT scanner. Colpohysterectomy plus pelvic lymphadenectomy was performed in 142 patients (92%). Among these, lumbo-aortic lymphadenectomy was performed in 103 patients (73%).

Guess of the dose rate

With regard to guessing the dose rate group, the surgeon guessed correctly in 54% of patients [95% confidence interval (CI) 45–62%]. This result was not significantly different than the expected 50% guesses under a random process. However, this result was dissimilar in each group with 74% correct guesses in the 0.38 Gy/h group and 32% in the 0.73 Gy/h group

($P < 0.001$). The surgeon associated surgical difficulties more frequently to the higher dose rate group, since overall only 29% of patients were assigned to the 0.73 Gy/h group by the surgeon.

When only patients with deferred surgery were analysed, the overall correct prediction rate was 58% (95% CI 48–67%), consistent with a random assignment process. Differences in treatment groups revealed 77 and 36% correct guesses, respectively, in the 0.38 Gy/h and 0.73 Gy/h groups ($P < 0.002$).

Surgical difficulties

The subgroup of patients with surgery performed more than 6 weeks following brachytherapy is, from a clinical point of view, different than the patient population with surgery performed less than 1 month following brachytherapy. In addition, the longer delay in surgery after brachytherapy gives the tumour more time to decrease in size and allows the postradiation congestive phenomena to decrease accordingly. Surgical difficulties were thus evaluated overall and separately for timing of surgery.

All patients. Overall surgical difficulties were noted for 39% of patients. These concerned problems with haemostasis in 28% of patients and difficulties in dissection in 34% of patients. Tumour size and dose rate and other variables significant at the $P = 0.10$ level of significance for any one of these criteria are presented in Table 3.

In a univariate analysis, more difficulties with haemostasis were observed for patients with previous surgery to the pelvic or abdominal region (41%), stage IIp (35%) and immediate surgery (41%). No significant variability in the percentage with haemostasis was observed for the following variables: age, endocervix involvement at brachytherapy, previous radiotherapy, lymph node involvement, tumour size at brachytherapy, split course brachytherapy and other brachytherapy parameters. The percentage of difficulties with haemostasis in each of the two treatment groups (23 versus 33%, respectively) was not statistically significant ($P = 0.16$).

In a multivariate analysis, immediate surgery ($P = 0.03$) and

Table 3. Surgical difficulties (univariate analysis)

	Difficulties with haemostasis (28%)	Difficulties in dissection (34%)	Surgical difficulties (39%)
Age (years)			
< 40	23%	26%	26%
40–59	28%	34%	41%
≥ 60	35%	46%	54%
P	ns	ns	0.06
Previous surgery			
No	24%	35%	37%
Yes	41%	32%	49%
P	0.05	ns	ns
Stage			
I	20%	26%	32%
II	35%	41%	46%
P	0.05	0.06	0.08
Involvement of endocervix			
No	29%	26%	33%
Yes	27%	41%	45%
P	ns	0.06	ns
Lymph node involvement			
N−	26%	29%	36%
N+	33%	48%	48%
P	ns	0.03	ns
Largest tumour dimension (mm)			
< 40	25%	30%	39%
40–59	32%	38%	40%
≥ 60	27%	38%	38%
P	ns	0.06	ns
Pear volume irradiation (cm^3)			
< 120	39%	54%	61%
120–179	29%	32%	40%
≥ 180	22%	27%	29%
P	ns	0.05	0.02
Surgery			
Deferred	24%	30%	35%
Immediate	45%	48%	52%
P	0.03	0.06	ns
Dose rate			
0.38 Gy/h	23%	31%	33%
0.73 Gy/h	33%	38%	45%
P	ns	ns	ns

ns, non-significant.

stage II ($P = 0.05$) were the most important prognostic factors for increasing problems with haemostasis. The dose rate effect was not significant when adjusted for these factors ($P = 0.23$). When endocervix involvement, which was different in the two dose rate groups, was also accounted for, the dose rate had no significant effect on haemostasis ($P = 0.16$).

In a univariate analysis, more difficulties in dissection were observed for stage IIp patients (41%), endocervix involvement (41%), positive lymph node involvement (48%), immediate surgery (48%), and a small pear volume irradiation (54% for a volume less than 120 cm^3; 60 Gy isodose). No significant variability in the percentage of difficulties in dissection was observed for the following variables: age, previous surgery or radiotherapy, tumour size at the start of brachytherapy, split course brachytherapy and other brachytherapy parameters. The percentage of difficulties in dissection in each of the two dose rate groups (31 versus 38%, respectively) was statistically non-significant ($P = 0.39$).

In a multivariate analysis, lymph node involvement ($P < 0.04$) was the most important prognostic factor for increasing difficulties in dissection. Stage, age, endocervix involvement and timing of surgery were not significant when adjusted for lymph node involvement. The dose rate effect was not significant when adjusted for lymph node involvement ($P = 0.55$). When endocervix involvement was also accounted for, the dose rate had no significant effect on difficulties in dissection ($P = 0.77$).

In a univariate analysis, more overall surgical difficulties were observed for patients aged 60 years or older (54%), stage IIp (46%), a small pear volume irradiation (61%). No significant variabilities in overall surgical difficulties were observed for the following variables: previous surgery or radiotherapy, endocervix involvement at brachytherapy, lymph node involvement, tumour size at brachytherapy, timing of surgery, split course brachytherapy and other brachytherapy parameters. The percentage of overall surgical difficulties of each of the two treatment groups (33 versus 45%, respectively) was statistically non-significant ($P = 0.13$).

In a multivariate analysis, pear volume ($P = 0.02$), age ($P = 0.05$) and stage ($P = 0.07$) were the most important prognostic factors for overall surgical difficulties. Pear volume still remained significant when adjusted for previous radiotherapy ($P = 0.02$). Its effect, however, was partially explained by age, since there was a negative correlation between age and pear volume: older patients were irradiated on a smaller volume.

The dose rate effect was not significant when adjusted for age and stage ($P = 0.15$). When endocervix involvement was also accounted for, the dose rate had no significant effect on overall surgical difficulties ($P = 0.25$).

Patients who received immediate surgery. No significant differences were observed between the 0.38 and 0.73 Gy/h dose rate groups.

Patients who received deferred surgery. More problems with haemostasis were observed for patients randomised to the higher dose rate group (31 versus 17%; $P = 0.08$). When stage was taken into account, this difference was at the limit of statistical significance ($P = 0.06$). This difference was essentially due to increased surgical difficulties in the 0.73 Gy/h group for stage IIp patients (41%), whereas only 17% of patients in the lower dose rate group experienced problems in haemostasis, irrespective of stage (Table 4).

Similar analyses were performed for difficulties in dissection and overall surgical difficulties. Similar surgical difficulties were encountered for stage I patients, irrespective of dose rate. In stage IIp patients, however, more surgical difficulties were encountered in the higher dose rate group ($P = 0.01$) (Table 4).

Sterilisation

All patients. Overall, the tumour was considered sterilised in 73 patients (47%, 95% CI 39–56%). Variables significantly correlated with sterilisation are presented in Table 5.

A univariate analysis indicated that factors associated with a lower rate of sterilisation were age less than 40 years (30% sterilisation), age 60 years or more (42%), previous radiotherapy (31%), large tumour size (19% for tumour size $\geq$ 6 cm), lymph node involvement (22%), split course brachytherapy (33%), large irradiated pear volume (33% for pear volume $\geq$ 180 cm^3) and immediate surgery (6%). Previous surgery to the pelvic or abdominal region, stage, endocervix involvement and other dosimetry variables were not correlated with sterilisation.

In the 0.73 Gy/h dose rate group, a 39% sterilisation rate was observed as opposed to 54% in the 0.38 Gy/h dose rate group in a univariate analysis. The difference in the rates of sterilisation between the two treatment groups was at the limit of statistical significance ($P = 0.07$).

A multivariate analysis indicated that the factors associated with a lower rate of sterilisation were immediate surgery

Table 4. Surgical difficulties in patients with deferred surgery adjusted for stage

	Difficulties with haemostasis (25%)	Difficulties in dissection (31%)	Surgical difficulties (37%)
Stage I	19%	24%	29%
0.38 Gy/h	17%	29%	31%
0.73 Gy/h	22%	17%	26%
P	—	ns	ns
Stage IIp	30%	38%	44%
0.38 Gy/h	17%	23%	27%
0.73 Gy/h	41%	50%	58%
P	—	0.03	0.01
P test for homogeneity	ns	0.03	0.04
Adjusted treatment comparison	0.06	—	—

ns, non-significant; —, statistical test not relevant.

Table 5. Sterilisation

	All patients (73/155=47%)	*P*	Deferred surgery (71/124=57%)	*P*
Age (years)				
< 40	13/43 (30%)		12/27 (44%)	
40–59	49/86 (57%)		49/74 (66%)	
≥ 60	11/26 (42%)	0.02	10/23 (43%)	0.05
Previous radiotherapy				
No	60/113 (53%)		58/94 (62%)	
Yes	13/42 (41%)	0.02	13/30 (43%)	0.08
Largest tumour dimension (mm)				
< 40	44/72 (61%)		44/66 (67%)	
40–59	24/57 (42%)		22/45 (49%)	
≥ 60	5/26 (19%)	0.001	5/13 (38%)	0.06
Lymph node involvement				
N−	63/109 (58%)		62/100 (62%)	
N+	10/46 (22%)	0.001	9/24 (38%)	0.03
Number of brachytherapy sessions				
1	55/100 (55%)		54/87 (62%)	
2	18/55 (33%)	0.007	17/37 (46%)	0.10
Pear volume (cm^3)				
< 120	14/28 (50%)		13/20 (65%)	
120–179	38/64 (59%)		38/57 (67%)	
≥ 180	21/63 (33%)	0.02	20/47 (43%)	0.03
Time of surgery				
Immediate	2/31 (6%)			
Deferred	71/124 (57%)	0.001		
Dose rate				
0.38 Gy/h	43/79 (54%)		42/65 (65%)	
0.73 Gy/h	30/76 (39%)	0.07	29/59 (49%)	0.09

($P < 0.003$), large tumour size ($P = 0.025$) and lymph node involvement ($P < 0.043$). Age, stage, endocervix involvement, previous radiotherapy, previous surgery, split course brachytherapy, pear volume and other brachytherapy parameters were not significantly prognostic of sterilisation, once the first three important variables were accounted for in the analysis. The difference in sterilisation rates between treatment groups, adjusted for timing of surgery, tumour size and lymph node involvement was not statistically significant ($P = 0.13$). Adjustment for endocervix involvement did not modify the results.

Patients who received deferred surgery. A second multivariate analysis was limited to the 124 patient subgroup with deferred surgery for reasons mentioned above. The overall sterilisation rate in patients with deferred surgery was 57% (95% CI 48–66%) (Table 5).

The univariate analysis limited to this subgroup of patients indicated that the factors associated with a lower percentage of sterilisation were previous radiotherapy (43% sterilisation), large tumour size (38% for tumour size ≥ 6 cm), lymph node involvement (38%), split course brachytherapy (46%), and large irradiated pear volume (43% for volume ≥ 180 cm^3). Age was not statistically significant, but a tendency for lower sterilisation rates among women aged under 40 or 60 or more was observed, with the highest sterilisation rate observed for the age group between 40 and 59 years (66%).

In the 0.73 Gy/h dose rate group, a 49% sterilisation rate was observed compared to 65% in the 0.38 Gy/h dose rate group. Although there was a tendency for a lower sterilisation rate in the higher dose rate group, the difference was statistically non-significant ($P = 0.09$).

In the multivariate analysis, large tumour size ($P = 0.03$) and lymph node involvement ($P = 0.05$) were significantly prognostic for lower sterilisation rates, as in the analysis on all patients. The treatment comparison, adjusted for these two variables was not statistically significant ($P = 0.12$). The inclusion of endocervix involvement in the model did not modify the results.

When dose rate was adjusted for tumour size and stage, a statistically significant difference was observed in patients with deferred surgery ($P = 0.04$). The rates of sterilisation between the dose rate groups were not significantly different for tumours less than 4 cm, nor for tumours greater than 6 cm. However, for tumour sizes in the middle range, only half as many tumours were considered sterilised in the 0.73 Gy group (26%) compared to the 0.38 Gy/h group (65%) ($P = 0.02$) (Table 6).

DISCUSSION

This randomised phase III trial included patients at a single centre over a little less than 4 years. The eligibility criteria were satisfied in 97% of cases; the patients who did not satisfy the criteria were equally divided between the two groups. In terms of the patient population, the study conditions may be considered quite satisfactory. The planned therapeutic protocol was adhered to for 87% of patients. Most of the deviations involved only surgery (10%), and the remaining 3% involved brachytherapy.

Table 6. Sterilisation adjusted for tumour size and stage (patients with deferred surgery)

	0.38 Gy/h (n = 65)	0.73 Gy/h (n = 59)	P
Tumour size: < 40 mm (n = 66)	70%	64%	
Stage I (n = 38)	58%	68%	
Stage IIp (n = 28)	86%	57%	ns
Tumour size: 40–59 mm (n = 45)	65%	26%	
Stage I (n = 17)	54%	25%	
Stage IIp (n = 28)	77%	27%	0.01
Tumour size: ≥ 60 mm (n = 13)	33%	43%	
Stage I (n = 4)	0%	0%	
(Stage IIp (n = 9)	67%	50%	ns

ns, non-significant.

Thus, the study conditions for a therapeutic trial were good. One of the major features of this trial is the homogeneity of the treatment protocol, thus eliminating procedural variations, as the techniques of brachytherapy and dose specification often vary from one centre to another [22, 23].

The analysis reported here is limited to patients irradiated and operated at IGR (76% of the overall population). This guarantees a homogeneity in the surgical procedure, and in the evaluation of the surgical difficulties and the sterilisation of the surgical specimen.

One of the principle questions underlined by this study concerns the influence of the dose rate on the surgery. From the overall results of this study, the length of irradiation for a given total dose did not influence the difficulties encountered during surgery. This was demonstrated by the fact that the surgeon could not correctly guess the treatment group, being prone to assign the higher dose rate when surgical difficulties were encountered, and by the fact that the dose rate was not a prognostic factor for overall surgical difficulties.

Nevertheless, in the subgroup of patients operated on more than 6 weeks after the end of brachytherapy, there was a tendency for there to be more problems with haemostasis in the higher dose rate group. These data are consistent with radiobiological experiences which predict that an increase in the dose rate mainly influences late effects, affecting early effects to a lesser extent [24, 25]. Indeed, the cumulative incidence of overall complications and side-effects as a first event observed after the start of brachytherapy has previously been shown to be significantly more frequent in the higher dose rate group [26].

These results are also consistent with data from a phase III study of interstitial brachytherapy for skin cancer patients, where no dose rate effect was observed on early skin reactions [27]. However, patients who received deferred surgery and were treated with the higher dose rate had a two-fold increase in surgical difficulties than those in the lower dose rate group. This effect was more pronounced for stage IIp patients, suggesting that patients irradiated over a larger volume required more extensive surgery.

A plausible explanation for all these findings is that there is a peak in early reactions to the radiation, the intensity of which cannot be distinguished at immediate surgery because the overall incidence of surgical difficulties is already relatively high, even in the lower dose rate group. However, later at delayed surgery, the difference in intensity between high and low dose rate groups can be detected, since those caused by the higher dose rate take longer to recede than those caused by the lower dose rate.

This study also investigated factors which may influence surgical difficulties when surgery is preceded by brachytherapy, especially the role of irradiation volume. Increased age and stage IIp were poor prognostic factors for surgical difficulties. However, fewer surgical difficulties were observed for patients irradiated over a large volume (P = 0.02), although this effect was partially explained by age, with older patients irradiated over a smaller volume. Nevertheless, it can be concluded that a large irradiated volume does not complicate surgery.

One of the arguments against pre-operative brachytherapy in cervical cancer patients is that it does complicate the surgery. However, Rampone [28], in a series on 537 patients with stage IB carcinoma of the cervix, noted that pre-operative brachytherapy allowed a less extensive ureteral dissection and smaller vaginal cuffer, which of course facilitates surgery. Our data appear to support this.

The association of surgical difficulties and the presence of residual tumour on the surgical specimen was also examined in this study. For some, tumour persistence after radiotherapy is an unfavourable prognostic factor, as is lymph node involvement [21, 29–34], while for others residual carcinoma of the cervix in the surgical specimen had no prognostic value [20, 35]. It is also worth mentioning that, with only histological examination of the specimen, it is difficult to assess viability of tumour cells following irradiation, since it has been shown that histological sections may show a morphologically intact tumour that will lack viable tumour cells on bio-assays [36].

However, in this study, only 47% of all the specimens, and 57% of those from deferred surgery, showed no residual tumour in the cervix. These sterilisation rates are less than those already in the literature, despite the fact that the dose delivered by brachytherapy was one of the highest used. There are three possible reasons for this.

Firstly, the number of serial sections of the specimen examined is critical, and as shown by Perez [3], a significant number of residual tumour cells may be overlooked in routine sections compared with multiple sections. In this study, 5 mm thick sagittal samples of the cervix, including all the fragments, were examined according to a strict protocol by the same team of pathologists, which is in contrast with examinations in previous studies.

Secondly, unlike other studies, this trial included patients who received surgery within 1 month or 6 weeks after brachytherapy. For assessment of the therapeutic response, delaying examination of tumours is typically justified on the basis that cell death would not be apparent until sufficient time had elapsed for the majority of the cells to divide. This point is illustrated by the fact that the most important independent factor for tumour sterilisation is the time elapsed between brachytherapy and surgery.

Finally, in this study, 53% of patients had tumours ≥ 40 mm, in contrast to most other series of smaller tumours. Thus, the role of tumour size is hardly surprising since there is likely to be more residual disease on a large tumour. In addition, with immediate surgery, the tumour does not have sufficient time to shrink, and so the rate of residual tumour is overestimated.

Another important parameter is lymph node involvement, which was shown to be a strong prognostic factor for sterilisation in this study. This was also the case when survival and relapse-free survival were used as endpoints [26]. A correlation between

residual tumour after brachytherapy and positive lymphoadenectomy had been reported previously [4, 20, 29], with Pilleron demonstrating a residual tumour rate of 40% for patients with lymph node involvement compared to 16% for the others [4].

Overall, the rate of tumour sterilisation was not significantly influenced by the dose rates compared in this study. This is in accordance with radiobiological data. The cell proliferation of squamous cell carcinomas is similar to those early responding normal tissues [37]. The dose per session (for doses of about 2 Gy) and the dose rate (especially for two dose rates as close as 0.73 and 0.37 Gy/h) have little influence on this type of tissue. Nevertheless, for a tumour size between 4 and 6 cm, the sterilisation rate was significantly higher in the lower dose rate group (Table 6).

During a low dose rate irradiation several biological processes occur. In terms of repair, a sparing effect of the lowest dose is expected, and from this point of view an inverse dose rate effect was observed for tumours in the middle range. Alternatively, reoxygenation could explain the increase in effectiveness of the lower dose rate. It is now well established that hypoxic cells exist in cervical cancer [38] and that tumour oxyenation is an important prognostic factor influencing radiocurability [39, 40]. After or during irradiation, reoxygenation can occur in a few hours or take several days to be completed. Therefore, the tumours treated for a longer time (i.e. a lower dose rate) are more likly to have less hypoxic radioresistant tumour cells. As hypoxia is more specific to solid tumours, this phenomenon is not expected to occur in normal tissues. Cao [41] also described an inverse dose rate effect, but as he irradiated mouse ascites sarcoma cells *in vivo* rather than solid tumours, he rejected the reoxygenation explanation. He suggested that cellular repair processes are induceable by radiation: very low dose rate (or very low doses) of X-rays would be more effective per gray than higher dose rates because only at a high dose rate is there sufficient damage to trigger repair systems or other radioprotective mechanisms at the cellular level. Several reports on induced repair processes on algae [42–44], plant cells *in vitro* [45], protozoan cells [46], insect cells [47, 48], mammalian cells [49, 50], human tumours cells [51], human lymphocytes [52], and mammalian tissues irradiated *in vivo* [53, 54] indicate the possibility that induceable repair may be a general biological phenomenon. Most of these studies relate to low dose, some of them low dose rate [41, 44, 55, 56]. With the exception of Cao [41], the dose rates producing an inverse dose rate effect are less than the lowest dose rate of this study (0.4 Gy/h), but this is not contradictory since the clinical concept of low dose rate is expressed as a mean value, which may obscure a heterogeneity in the true dose rate delivered (and hence of dose). In fact, the dose rate close to the source is high and the total dose delivered is also high, so most of the cells will be killed. Further away from the sources, both the dose rate and the total dose decrease. Thus, in the lower dose rate group, tumour cells were further from the radioactive sources and, therefore were irradiated at a very low dose rate, compared to the 0.8 Gy/h group. This very low dose rate, however, may be more effective in killing the cells because there is no repair induction. This effect is expected to be more important on large tumours in which more cells are further from the radioactive sources, although there must be an upper limit beyond which the chance of sterilisation would be reduced.

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